Pharmacokinetic and Pharmacodynamic Modeling of Acetylsalicylic Acid and its Major Metabolite Salicylic Acid

UNIVERSITÄT DES SAARLANDES

Christiane Dings[1], Thorsten Lehr[1]

[1]Clinical Pharmacy, Saarland University, Saarbrücken, Germany

BACKGROUND AND OBJECTIVES

Acetylsalicylic acid (ASA) is a well-known antipyretic drug and has been studied and used for its anti-thrombotic effect since the 1960s [1]. The inhibition of cyclooxygenase (COX) by ASA as the main mechanism of action in platelets is well studied. However, there is little knowledge about the pharmacokinetic/pharmacodynamic (PK/PD) relationship between ASA and platelet aggregation.

The aim of the work was to develop a PK/PD model of ASA and its major metabolite salicylic acid (SA) including thromboxane B2 (TxB2) as the metabolite of thromboxane A2 (TxA2) and therefore as the biomarker for the antithrombotic effect of ASA.

METHODS

Mean profiles were digitized from a study comparing PK and PD after doses of 5 to 80 mg ASA as instant release (IR) and 20 to 325 mg as extended release (ER) formulations in 50 volunteers [2]. The data included 70 and 85 mean plasma concentrations of ASA and SA, respectively, and 77 mean measurements of TxB2 inhibition. The model was evaluated using digitized data from another PK/PD study [3]. Deterministic simulations were performed to investigate different treatment regimens ensuring sufficient inhibition of the platelet aggregation throughout the day (≥95% inhibition at steady-state) [3]. Modeling and simulation were performed using NONMEM V7.2.0 without interindividual variability, considering residual variability.

RESULTS

Model: For ASA and SA a one- and two-compartment model, respectively, described the pharmacokinetics best. An additional compartment between the absorption compartment and the central compartments of ASA and SA was included to describe the presystemic metabolism and pharmacodynamic effect of ASA. All absorption, distribution and elimination processes of ASA and SA were described as first-order processes.

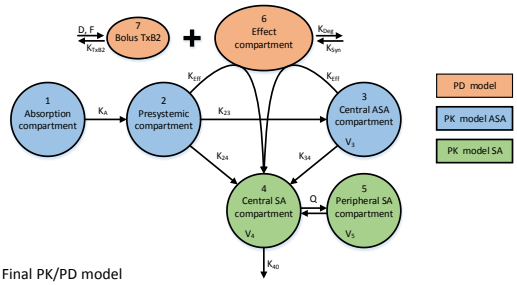

Figure 1. Final PK/PD model

TxB2 levels were described by a turnover model with zero-order input and first-order output. Under ASA treatment a second-order elimination depending on ASA and TxB2 levels was incorporated. For smaller doses, drops in the TxB2 levels were observed, indicating a bulk release of TxB2. To account for this, a compartment with a zero-order bolus input at the time of ASA dosing and a first-order output was added (Figure 1, Table 1).

Table 1. Parameter estimates of the final PK/PD model

Parameter	Value (RSE* [%])	Description
K_A (IR) [h^{-1}]	1.32 (16.6)	First-order absorption rate constant for IR tablet
K_A (ER) [h^{-1}]	0.121 (4.2)	First-order absorption rate constant for ER tablet
ALAG (IR) [h]	0.103 (7.0)	Lag-time for the absorption for IR tablet
ALAG (ER) [h]	0**	Lag-time for the absorption for ER tablet
K_{23} [h^{-1}]	0.554 (20.4)	First-order distribution rate constant between Comp. 2 and 3
K_{24} [h^{-1}]	0.566 (13.5)	First-order distribution rate constant between Comp. 2 and 4
V_3 [L]	10.5**	Volume of distribution of ASA
V_4 [L]	9.92**	Volume of distribution of central SA
V_5 [L]	1.98 (28.3)	Volume of distribution of peripheral SA
Q [L h^{-1}]	0.0796 (39.8)	Intercompartmental clearance
K_{34} [h^{-1}]	5.04 (12.8)	First-order metabolism rate constant for ASA
K_{40} [h^{-1}]	0.435 (6.2)	First-order elimination rate constant for SA
BASE [mmol]	2.18×10^{-9}**	Baseline amount in effect compartment
K_{Deg} [h^{-1}]	0.0049**	First-order degradation rate constant in effect compartment
K_{Syn} [mmol h^{-1}]	1.1×10^{-11}**	Second-order synthesis rate constant in effect compartment
K_{Eff} [$mmol^{-1}$ h^{-1}]	4.62×10^{-9} (21.6)	Second-order rate constant for the acetylation of COX by ASA
F	3.25 (15.0)	Bioavailability for bolus infusion of TxB2 at time 0
D [h]	1 (0.0)	Duration of bolus infusion of TxB2 at time 0
K_{TxB2} [h^{-1}]	6.9**	First-order rate constant for infused TxB2
PRV ASA (CV%)	18.7 (17.4)	Proportional residual variability of ASA
PRV SA (CV%)	2.19 (19.2)	Proportional residual variability of SA
ARV SA (SD)	0.00132 (32.2)	Additive residual variability of SA
PRV TxB2 (CV%)	278 (21.1)	Proportional residual variability of TxB2

*Residual standard error; **Fixed

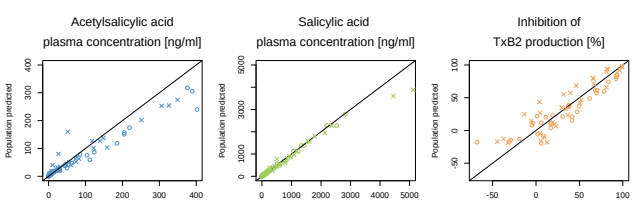

Figure 2. Goodness-of-fit plots: Population predicted vs. observed for IR formulation (circles) and ER formulation (crosses). Black lines are lines of identity.

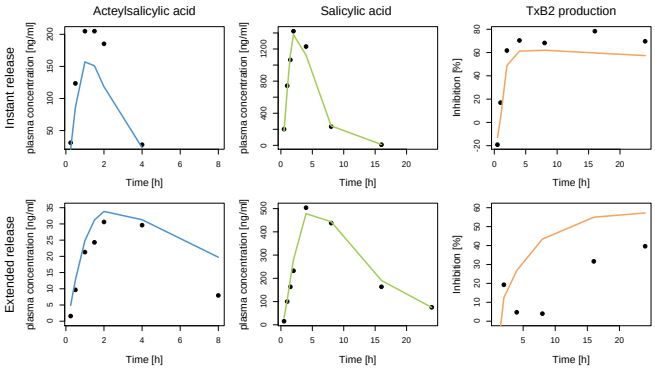

Figure 3. Concentration-time profiles administration of 40 mg ASA from the development dataset (points) and model predictions (line).

Evaluation: Goodness-of-fit plots and some concentration-time profiles can be seen in Figures 2 and 3. In the study used for the evaluation dataset, TxB2 levels were measured differently. After adjustment of the parameters K_A and K_{Deg} due to the change in methods, the model successfully predicted the plasma TxB2 levels of the evaluation dataset (Figure 4).

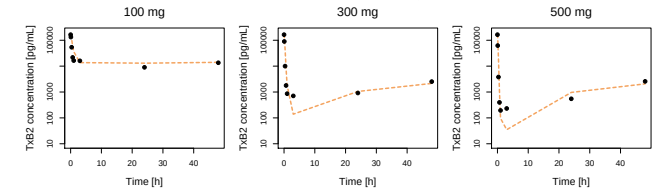

Figure 4. Concentration-time profiles for different doses from evaluation dataset (points) and model prediction (line) for TxB2.

Simulations: The administration of 97 mg IR-ASA twice daily and 169 mg ER-ASA once or 49 mg ER-ASA twice daily resulted in a sufficient inhibition of platelet aggregation over the period of 24 hours in steady-state. Peak ASA plasma levels ensuring sufficient platelet inhibition were lower for the ER compared to the IR formulation (Figure 5).

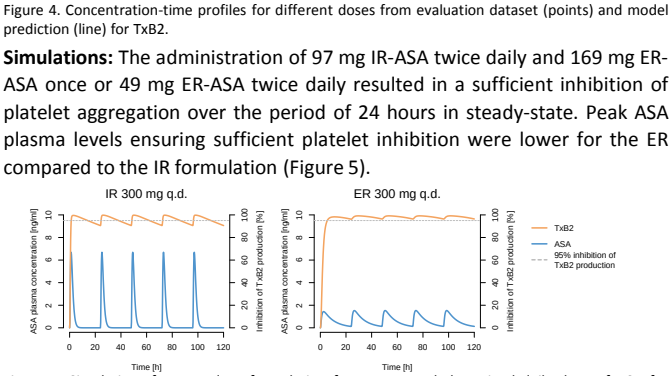

Figure 5. Simulations for IR and ER formulation for recommended maximal daily dose of ASA for stroke prevention [4]. Blue lines indicate ASA levels, orange lines indicate inhibition of TxB2 production and grey dashed lines indicate 95% inhibition of TxB2 production.

CONCLUSION

A PK/PD model for ASA and its major metabolite SA was presented for the first time. The model demonstrated a good predictive performance. Deterministic simulations confirmed an advantage of the ER formulation over the IR formulation.

REFERENCES:

[1] Weiss H J et al. *The discovery of the antiplatelet effect of aspirin: a personal reminiscence*. **2003**

[2] Patrick J et al. *A randomized trial to assess the PD and PK of a single dose of an extended-release aspirin formulation*. **2015**

[3] Nagelschmitz J et al. *PK and PD of acetylsalicylic acid after intravenous and oral administration to healthy volunteers*. **2014**

[4] Endres M et al. *Sekundärprophylaxe ischämischer Schlaganfall und transistorische ischämische Attacke*. **2015**